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EDGEWOOD ARSENAL
TECHNICAL REPORT

EATR 4311

ALKYLATION OF AMINES

A NEW METHOD FOR THE SYNTHESIS OF QUATERNARY AMMONIUM COMPOUNDS FROM PRIMARY AND SECONDARY AMINES

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Harold Z. Sommer
Larry L. Jackson

July 1969

DEPARTMENT OF THE ARMY
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Edgewood Arsenal, Maryland 21010

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Harold Z. Sommer
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Task 1B56260A06008

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FOREWORD

The work described in this report was performed under Task 1B56260A06008, Chemical Agents, Incapacitating Agents. The experimental data are recorded in notebooks 7123, 7921, 8109, 7920, and 8085. The work was started in October 1967 and completed December 1968.

Acknowledgments

The authors are indebted to Mr. Ronald D. Deibel for his valuable assistance in the experimental work and to Mr. C.A. Rush, Mr. J.M. Corliss, Mr. S.S. Cruikshank, Mr. E.J.W. Rhodes, Mrs. M.F. Buckles, and Mrs. N.B. Scholtz, Analytical Chemistry Department, for the microanalyses.

DIGEST

A new method for the preparation of quaternary ammonium compounds by complete alkylation of primary or secondary amines to their quaternary stage in a one-step procedure is described. The observation that protonation of sterically hindered amines is only slightly affected by steric hindrance, whereas nucleophilicity as measured by the rate of alkylation is considerably decreased, is synthetically utilized. An organic base of greater base strength than the reactant amines is employed to bind the acid generated in alkylation reactions. Thus, a number of aniline derivatives are methylated in the presence of the stronger, but sterically hindered base 2,6-lutidine. The mild and homogenous reaction conditions result in good yields with minimal laboratory manipulations and effort. The method is particularly of importance in reactions where the amines and the alkylating agents possess labile functions.

CONTENTS

ALKYLATION OF AMINES
A NEW METHOD FOR THE SYNTHESIS OF QUATERNARY AMMONIUM COMPOUNDS FROM PRIMARY AND SECONDARY AMINES

I. INTRODUCTION.

Quaternary ammonium compounds occur widely in nature and have found application both in the laboratory and in industry. The quaternary neurohormone, acetylcholine, for example, plays a vital role in most living organisms. In the laboratory, they are of interest particularly as intermediates in organic synthesis. The Stevens rearrangement, the Sommelet rearrangement, the Hofmann degradation, and the preparation of tertiary amines by pyrolysis require quaternary ammonium compounds. Industrially, large quantities are produced for use as detergents, insecticides, bacteriostats, drugs, and as intermediates in various synthetic processes.

Quaternary ammonium compounds are prepared in most cases from tertiary amines, primary or secondary amines being used only occasionally as the starting materials.[1-3] The methods previously available for direct alkylation of primary and secondary amines to the quaternary stage require relatively harsh reaction conditions and give rise to undesirable side reactions; thus, they are limited to stable amines and alkylating agents. These methods were developed by A.W. Hofmann in the nineteenth century, and are still employed without significant changes. The reaction of a primary or secondary amine with an alkylating agent, such as an alkyl halide, involves the liberation of a hydrohalic acid which combines with the reactant amines to form a mixture of amine hydrohalide salts. Consequently, very low concentrations of free amines remain for subsequent alkylation. To increase the concentration of the free amines, inorganic bases are utilized as the proton acceptors.

The general procedure for the direct alkylation of primary or secondary amines to their quaternary ammonium salts is to reflux a mixture of the amine, an excess of the alkyl halide, and sodium carbonate or sodium hydroxide in water or alcohol. Under these heterogenous reaction conditions prolonged heating is needed, leading to numerous side reactions and low yields. Consequently this method is of value only in those instances where both the amines and the alkylating agents are thermally stable and are insensitive to strong inorganic bases. Further complications arise from the fact that the physical properties of quaternary ammonium salts closely resemble those of inorganic salts. Thus, the purification of quaternary compounds in the presence of inorganic salts can be very laborious and time consuming, since their solubilities in most common solvents are very similar. In view of the above difficulties and in spite of the additional steps involved, the route usually chosen is the synthesis and isolation of the appropriate tertiary amine prior to quaternization.

This report describes a new method for the preparation of quaternary ammonium compounds by direct alkylation of primary and secondary amines to their quaternary stage in a one step procedure. The mild and homogenous reaction conditions employed result in good yields with minimal laboratory manipulations and effort. The new method is also applicable to amines and alkylating agents that possess labile functions. Therefore, quaternary products with reactive moieties that cannot be obtained, or are prepared with difficulty at best, by the conventional exhaustive alkylation methods can be prepared with relative ease. Furthermore, the usually more accessable primary and secondary amines can now serve to a much larger extent in the synthesis of quaternary compounds.

II. DISCUSSION AND RESULTS.

When primary amines react with alkylating agents a sequence of reactions occurs resulting in the formation of a mixture of products.[4] The alkylations which are presumed to proceed by an Sn2 mechanism are schematically depicted as follows:

$$RNH_2 + R'X \underset{k_2}{\overset{k_1}{\rightleftharpoons}} [RR'NH_2]^+ X^- \underset{k_4}{\overset{k_3}{\rightleftharpoons}} RR'NH + HX$$

$$HX + RNH_2 \underset{k_6}{\overset{k_5}{\rightleftharpoons}} [RNH_3]^+ X^-$$

$$RR'NH + R'X \underset{k_8}{\overset{k_7}{\rightleftharpoons}} [RR'_2NH]^+ X^- \underset{k_{10}}{\overset{k_9}{\rightleftharpoons}} RR'_2N + HX$$

$$RR'_2N + R'X \underset{k_{12}}{\overset{k_{11}}{\rightleftharpoons}} [RR'_3N]^+ X^-$$

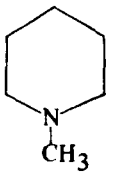
The composition of the product mixture depends on the molar concentration of the reactants, temperature, the basicities of the starting and alkylated amines, the steric configuration of all the reacting species, and their solubilities in the various solvent media. In the above complex series of equilibria the most readily controllable step is the final alkylation of the tertiary amine to the quaternary salt. The preparation of secondary and tertiary amines by this procedure is generally impractical because of the competing reactions and difficulty of separation. The equilibria can be shifted toward complete alkylation by the introduction of strong inorganic bases, but the disadvantages mentioned previously limit the scope of this approach.

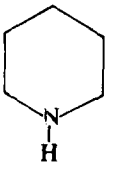
In principle, the alkylation of a primary or secondary amine to the quaternary stage could be greatly simplified if an organic base could be used to bind the acid that is generated as the reaction proceeds. The organic base should have solubilities similar to those of the starting amines in order to attain homogenous reaction conditions, it must be a stronger base (larger pKa) than the reacting amines in order to combine preferentially with the acid produced, it must alkylate at a significantly slower rate than the reacting amines, and it should be readily available. Preferably, the acid salt of the organic base and the quaternary ammonium salt should be separable on the basis of solubility.

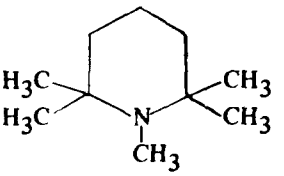
The seemingly contradictory requirements, that the organic base have a larger pKa, yet react at a slower rate than the amines to be alkylated, led us to examine more closely the relationship between basicity and nucleophilicity.

Correlations between basicity and nucleophilicity in amines have been extensively explored in the literature.[5-17] Even though a direct relationship has been demonstrated in most studies, the exceptions, attributable to steric hindrance, are of special interest.[7,11,13,14]

Hall[18] determined the basicities of the following piperidine compounds which are shown in the order of increasing pKa's:







pKa: 10.13 11.05 11.25

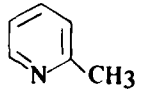
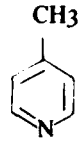
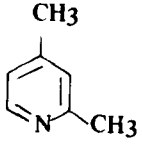
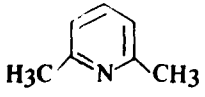
1-Methylpiperidine is a weaker base than piperidine, while 1,2,2,6,6-pentamethylpiperidine is the strongest of the three, in spite of the five methyl groups surrounding the nitrogen. These examples indicate, that whereas steric factors can weaken basicity, polar effects, however, overcome severe steric hindrance.

Such compensation is not encountered when the parameters that govern nucleophilicity are evaluated. Clarke and Rothwell[7] studied the effects of substituents on the rate of formation of alkylpyridinium halides. Selected data from their investigation are shown in table I.

Table I reveals that the basicity of the pyridine nitrogen is enhanced by the inductive effects of the alkyl substituents on the aromatic ring and that the influence of steric hindrance is insignificant. The pKa values of the monosubstituted 2- and 4-methyl pyridines (5.97 and 6.02) are essentially identical and greater by approximately 0.8 pKa unit than pyridine (5.17). Dimethyl substitution, both in the 2,4 and 2,6 positions, likewise results in very similar pKa values (6.72 and 6.77). The pKa of collidine, the 2,4,6-trimethyl pyridine derivative, rises to a value of 7.48. The additive effect of the methyl groups on base strength, an increase of about 0.8 pKa unit per methyl group from mono- to di- to trimethyl substitution, clearly demonstrates the electron donor feature and rules out steric hindrance as a significant factor in protonation.[11,13,14]

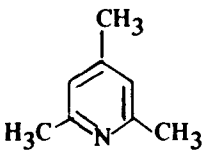
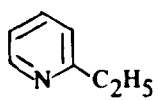
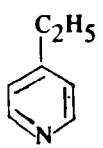
In sharp contrast, steric hindrance greatly affects nucleophilicity in these alkyl substituted pyridines. Of the cases cited, only 4-methyl and 4-ethylpyridine quaternize faster than pyridine. Regardless of base strength, the amines with *ortho* substituents alkylate slower. 2,6-Lutidine (pKa = 6.77) quaternizes with methyl iodide 18.6 times and 2,4,6-collidine (pKa = 7.48) 9.1 times slower than pyridine (pKa = 5.17). With allyl bromide the differences in alkylation rates are 260 and 150, respectively.

Table 1. PKa Values and Rate Constants for the Reactions of Pyridine Bases with Methyl Iodide and Allyl Bromide in Nitromethane

Compound	Basicity* (pKa)	Reaction Rate** $\times 10^4$ CH_3I	Comparative Nucleophilicity $\frac{k\ \text{pyridine}}{k}$ CH_3I	Reaction Rate** $\times 10^4$ $CH_2=CH-CH_2Br$	Comparative Nucleophilicity $\frac{k\ \text{pyridine}}{k}$ $CH_2=CH-CH_2Br$
	5.17	62.5	1	46.3	1
	5.97	31.3	2	7.53	6.2
	6.02	111.0	0.56	81.7	0.57
	6.72	–	–	14.6	3.2
	6.77	3.36	18.6	0.18	260

*At 20°C
**At 60°C

Table I. Continued

Compound	Basicity* (pKa)	Reaction Rate** $\times 10^4$ CH_3I	Comparative Nucleophilicity k pyridine k CH_3I	Reaction Rate** $\times 10^4$ $CH_2{=}CH{-}CH_2Br$	Comparative Nucleophilicity k pyridine k $CH_2{=}CH{-}CH_2Br$
	7.48	6.84	9.1	0.31	150
	5.99	17.1	3.7	3.65	12.7
	6.02	122.7	0.51	85.0	0.55

*At 20°C
**At 60°C

Numerous publications[5,8,10,19-23] deal with substituent effects on aniline and its derivatives. In *meta* and *para* substitution, the factors which control base strength closely parallel those that determine nucleophilicity. This direct relationship fails when applied to *ortho* substitution. The so-called "ortho effect," it is suggested, results from steric hindrance which is negligible in the *meta* and *para* positions.

When both steric and electrical effects have to be considered, it seems evident, that the latter is the dominant contributor in the determination of base strength, exemplified by the extremely hindered 1,2,2,6,6-pentamethylpiperidine, which is a 13 times stronger base than 1 methylpiperidine.[18] Steric effects, however, play the major role in the determination of nucleophilicity, strikingly demonstrated by the comparison of base strengths and alkylation rates of 2,6-lutidine and pyridine. 2,6-Lutidine is about 40 times stronger than pyridine in base strength, yet reacts with methyl iodide approximately 19 times slower.[7] Thus, competing strong electron donor and pronounced steric effects result in an increase of basicity and decrease of nucleophilicity.

In light of these observations the interaction between a proton and a hindered amine and the interaction of the same amine with an alkylating agent must be substantially different. The proton, due to its small size and its electron deficiency, appears to be able to approach the nitrogen of an amine and form a chemical bond in spite of steric hindrance. On the other hand, a sterically hindered nucleophile is hampered or even completely blocked in its attack on the alkylating agent. Whereas electron-donating groups favor the protonation of the amine, the inherent bulk of these groups retards alkylation. Severely hindered amines, it can be concluded, exhibit an inverse relationship between basicity and nucleophilicity.

In the search for an organic base that is readily protonated, yet is a relatively poor nucleophile, an appropriate hindered amine can now be chosen which can successfully serve as the proton acceptor in direct alkylation reactions of primary or secondary amines to their quaternary stage. The quaternization of aniline and its substituted derivatives with methyl iodide in the presence of 2,6-lutidine has been selected in the present study to test the validity and practical implementation of the above concepts. 2,6-Lutidine fulfills the requirements outlined for the organic base. Its pKa (6.77)[7] is greater than that of aniline (4.65),[10] *N*-methylaniline (4.89),[10] and *N,N*-dimethylaniline (5.07),[10] and is alkylated at a slower rate.[24] It is soluble in most common organic solvents, is commercially available, and the separation of trimethylphenylammonium iodide and 2,6-lutidine hydroiodide is feasible on the basis of solubility differences as shown in table II.

The concentrations of the reactants and the selection of the solvent are important for separation and purification of the quaternary ammonium salt. Table III lists the yields of trimethylphenylammonium iodide obtained at various concentrations in several solvents. A solution of aniline (1 equivalent), 2,6-lutidine (2 equivalents) and methyl iodide (excess) was allowed to stand at room temperature until precipitation of the product was complete. The product was collected and its purity determined by its melting point, and its mixed melting point with lutidine methiodide and lutidine hydroiodide.

Aniline generates two equivalents of hydroiodic acid when it is alkylated to the quaternary state with methyl iodide. Therefore, two equivalents of 2,6-lutidine are required to free the intermediate secondary and tertiary amines from their hydroiodides. While an excess of the alkylating agent is desirable, an excess of the proton acceptor should be avoided to minimize the formation of 2,6-lutidine methiodide.

Table II*. Solubilities of Trimethylphenylammonium Iodide and 2,6-Lutidine Salts

Compound	DMF 25°C	Acetone 25°C gm/100 ml	Acetone 56°C
Trimethylphenylammonium Iodide	13	0.15	0.5
2,6-Lutidine, Hydroiodide	60	2.5	7.0
1-Methyl-2,6-lutidinium iodide	6	0.16	0.4

*The data were obtained by saturating the solvent with a known quantity of the salt and weighing the undissolved material.

Table III. Yields of Trimethylphenylammonium Iodide as a Function of Concentration in Various Solvents at 25°

Solvent	Molar Concentration of Aniline	Yield (percent)
Acetone	0.054	0
Acetone	0.108	76
Acetone	0.215	Mixture*
DMF**	0.54	0
DMF**	0.90	28
DMF**	1.28	49
DMF**	1.54	59
DMF**	2.69	Mixture*
Methyl alcohol	0.54	22
Methyl alcohol	0.72	29
Methyl alcohol	1.20	39
Methyl alcohol	2.15	49
Methyl alcohol	3.58	52
Methyl alcohol	10.8	Mixture*
Acetonitrile	0.54	29
Acetonitrile	0.67	29
Acetonitrile	0.90	Mixture*
Ethyl acetate	0.108	Mixture*
Ethyl acetate	0.215	Mixture*
Benzene	0.154	Mixture*

*The mixture consists of Trimethylphenylammonium iodide and 2,6-lutidine, hydroiodide.

**_N,N_-Dimethylformamide.

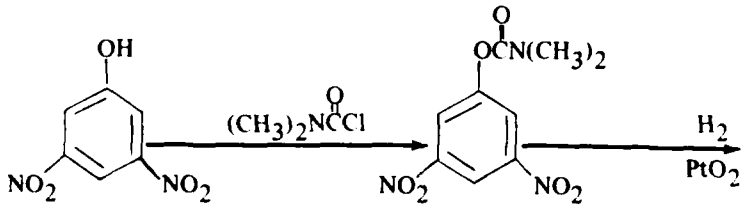
The above method has been successfully applied to aromatic amines in the pKa range from 3.86 (*p*-bromoaniline[9]) to 5.34 (*p*-anisidine[9]) as shown in table IV. The reaction with *m*-nitroaniline (pKa of 2.45)[25] resulted in a mixture of the desired product together with significant amounts of 2,6-lutidine methiodide. Hence, the lower limit of the usefulness of 2,6-lutidine in this quaternization method appears to be for amines with pKa's between 2.45 and 3.86. The upper limit is determined by the basicity of 2,6-lutidine; i.e., pKa of 6.77.

At the concentrations indicated in table IV, the quaternary ammonium product precipitates from the reaction solution. Higher concentrations often lead to mixtures and lower concentrations allow a substantial portion of the product to remain in solution.

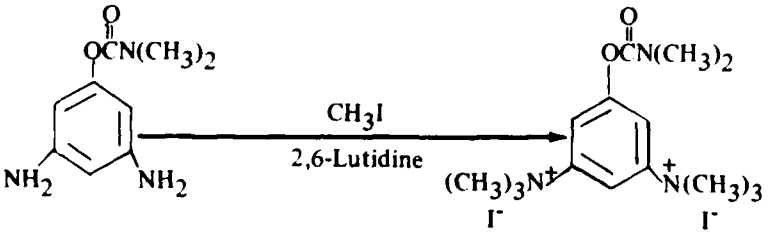
Amines can also be employed in the form of their salts, in which case three equivalents of 2,6-lutidine are used. The additional equivalent liberates the amine before alkylation proceeds. (*p*-Bromophenyl)trimethylammonium iodide has been prepared in this manner from *p*-bromoaniline hydrochloride.

When *N*-phenylbenzylamine (pKa of 4.04) was alkylated to form benzyldimethylphenylammonium iodide, a mixture containing 25 percent of 2,6-lutidine methiodide was obtained. In this instance, the steric hindrance of the starting secondary amine apparently is sufficient to decrease the alkylation rate to a level where 2,6-lutidine methiodide formation becomes significant. However, the mixture is easily separated on the basis of the relatively low solubility of 2,6-lutidine methiodide in methanol.

As examples for direct quaternization of amines possessing labile functions (*m*-hydroxyphenyl)trimethylammonium iodide, dimethylcarbamate (Prostigmine iodide) and the bisquaternary carbamate (5-hydroxy-*m*-phenylene)bis[trimethylammonium iodide], dimethylcarbamate (IV) were synthesized. The former was prepared from the dimethylcarbamate ester of *m*-aminophenol, and the latter as follows:

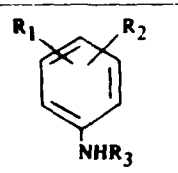
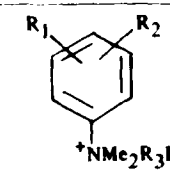


(I) (II)



(III) (IV)

Table IV. Aniline Derivatives Quaternized with Methyl Iodide in the Presence of 2,6-Lutidine

									
						Product			
R_1	R_2	R_3	pKa	Solvent	Molar Concentration Aniline Derivatives	R_1	R_2	R_3	Yield[a]
H	H	H	4.65[10]	Acetone	0.054	H	H	Me	76
p–Me[b]	H	H	5.08[25]	Methanol	2.16	*p*–Me	H	Me	53
p–OMe	H	H	5.34[9]	DMF[c]	1.53	*p*–OMe	H	Me	87
p–Br	H	H,HCl	–	Acetone	0.108	*p* Br	H	Me	76
p–Br	H	H	3.86[9]	DMF	2.09	*p* Br	H	Me	97
p–OH	H	H	5.31[26]	DMF	2.18	*p* OH	H	Me	60
m–OH	H	H	4.31[25]	DMF	2.18	*m* OH	H	Me	66
H	H	Me	4.89[10]	Methanol	2.70	H	H	Me	67
H	H	Benzyl	4.04[10]	Methanol	2.20	H	H	Benzyl	71
m–NH_2	H	H	4.88[27]	DMF	2.15	*m*–$\overset{+}{N}Me_3I^-$	H	Me	67
3 NH_2	5–$OCONMe_2$	H		DMF	0.40	3–$\overset{+}{N}Me_3I^-$	5–$OCONMe_2$	Me	63
m–$OCONMe_2$	H	H		Methanol	0.58	*m* $OCONMe_2$	H	Me	94

[a] Analytically pure material

[b] Me = methyl

[c] *N,N*-Dimethylformamide

If an anion other than iodide is desired the quaternary ammonium iodide is easily exchanged by conventional ion exchange procedures.[3]

This study is being continued to extend the applicability of the method described herein to a wider range of amines and alkylating agents.

III. EXPERIMENTAL.

A. Materials.

The aniline derivatives were distilled or recrystallized as required. 2,6-Lutidine and the solvents were dried and distilled before use.

B. General Procedure.

Methyl iodide (excess) was added to a solution of aniline or the aniline derivative and 2,6-lutidine in an appropriate solvent (see table III) at room temperature. The quaternary ammonium salt generally precipitates after a few hours. The product was collected, washed with acetone, and vacuum dried. To obtain analytically pure materials, the quaternary ammonium salts were stirred with additional acetone to remove any remaining 2,6-lutidine hydroiodide, or were recrystallized from acetone or a methanol-ether mixture. Known quaternary ammonium iodides were identified by their elemental analyses and melting points.[28,29] Analytical data and melting points of compounds not found in the literature are given in table V.

The reactions are exothermic and are often complete in a few minutes. Slow addition of methyl iodide or external cooling is, therefore, advisable. Dry solvents are essential since the presence of water greatly increases the solubility of quaternary ammonium compounds in organic solvents.

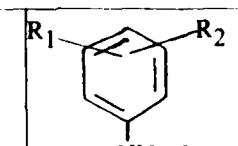
C. (5-Hydroxy-*m*-phenylene)bis[trimethylammonium iodide], dimethylcarbamate (IV).

A solution of 3.95 grams of 3,5-dinitrophenol (I), 2.33 grams of dimethylcarbamoyl chloride and 4 ml of triethylamine in 100 ml of benzene was refluxed for 4 hours. Triethylamine hydrochloride was removed by filtration and the filtrate washed with 0.1N sodium hydroxide and dried over sodium sulfate. Addition of 20 ml of ethanol precipitated crude 3,5-dinitrophenol, dimethylcarbamate (II). Recrystallization from ethanol-water gave 2.83 grams (52 percent) of yellow crystals: mp 78° to 79°C. *Anal.* Calculate for $C_9H_9N_3O_6$: C, 42.4; H, 3.5; N, 16.5. Found: C, 42.7; H, 3.5; N, 16.3.

A mixture of 510 mg of 3,5-dinitrophenol, dimethylcarbamate (II), and 200 mg of platinum oxide, and 20 ml absolute ethanol was hydrogenated in a Parr apparatus.* Absorption of 6 moles of hydrogen was complete in 20 minutes. The catalyst was removed by filtration and the filtrate evaporated to give 3,5-diaminophenol, dimethylcarbamate (ester) (III) as a residue. The residue was dissolved in 5 ml of *N,N*-dimethylformamide.

*Parr Instrument Company, Inc., Moline, Illinois.

Table V. Analytical Data

R_1	R_2	mp* °C	 Formula	Analyses							
				Calculated				Found			
				C	H	I	N	C	H	I	N
				(percent)				(percent)			
p–OMe	H	229	$C_{10}H_{16}INO$	41.0	5.5	43.3	4.8	41.2	5.6	43.2	4.9
m–$\overset{+}{N}Me_3I^-$	H	183	$C_{12}H_{22}I_2N_2$	32.2	5.0	56.6	6.2	32.0	5.2	56.6	6.3
3–$\overset{+}{N}Me_3I^-$	5–OCONMe$_2$	184	$C_{15}H_{27}I_2N_3O_2$	33.7	5.1	47.4	–	33.7	5.3	47.0	–

*Melting points are uncorrected.

2,6-Lutidine (0.9 ml) and methyl iodide (8 grams) were added and the solution allowed to stand at room temperature for 12 hours. The precipitate that formed was collected on a filter. Recrystallization from methanol-ether gave 670 mg (63 percent) of (5-hydroxy-*m*-phenylene)bis[trimethylammonium iodide], dimethylcarbamate (IV). *Anal.* See table V.

IV. CONCLUSIONS.

Primary and secondary amines have been exhaustively alkylated to their quaternary stage in a one step procedure.

The observation that protonation of sterically hindered amines is only slightly affected by steric hindrance, whereas nucleophilicity as measured by the rate of alkylation is considerably decreased, has been synthetically utilized. An organic base of greater base strength than the reactant amines has been employed to bind the acid generated in alkylation reactions.

Aniline and aniline derivatives with pKa's ranging from 3.86 to 5.34 have been completely methylated in the presence of the stronger, but sterically hindered base 2,6-lutidine (pKa of 6.77).

The mild and homogenous reaction conditions resulted in good yields with minimal laboratory manipulations and effort.

As an example of the applicability of the method to amines that possess labile functions the bisquaternary carbamate (5-hydroxy-*m*-phenylene)bis[trimethylammonium iodide], dimethylcarbamate has been prepared from 3,5-diaminophenol, dimethylcarbamate (ester) in a one step procedure.

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13. ABSTRACT

(U) A new method for the preparation of quaternary ammonium compounds by complete alkylation of primary or secondary amines to their quaternary stage in a one-step procedure is described. The observation that protonation of sterically hindered amines is only slightly affected by steric hindrance, whereas nucleophilicity as measured by the rate of alkylation is considerably decreased, is synthetically utilized. An organic base of greater base strength than the reactant amines is employed to bind the acid generated in alkylation reactions. Thus, a number of aniline derivatives are methylated in the presence of the stronger, but sterically hindered base 2,6-lutidine. The mild and homogenous reaction conditions result in good yields with minimal laboratory manipulations and effort. The method is particularly of importance in reactions where the amines and the alkylating agents possess labile functions.

14. (U) KEYWORDS

Alkylation
Quaternization
Amines
Steric hindrance
Basicity
Nucleophilicity
Alkylating agents
Aniline
Aniline derivatives
Carbamates
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